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DIPEPTIDYL PEPTIDASE-4 INHIBITORS INDUCED BULLOUS PEMPHIGOID: A REVIEW OF CURRENT CONCEPTS

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Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal blistering disease observed primarily in the elderly. Over the past two decades, there has been a substantial increase in BP incidence and prevalence in several countries worldwide. The reasons driving these increases include an increase in average life expectancy, better diagnostic methods, recognition of atypical variants of BP, and increased use of certain medications.

Drug-associated BP (DABP) is a term used to describe cases of BP demonstrating clinical, histological, or immunopathological features identical or similar to those of the idiopathic form of BP, but associated with the systemic ingestion or topical application of particular drugs. Since the first report of DABP in 1970, more than 90 individual drugs have been reported associated with BP so far. The strongest evidence of an association with DABP is found in dipeptidyl peptidase-4 inhibitors, also known as gliptins, a relatively new class of oral antidiabetics.

DABP should be considered a possible diagnosis in patients who have recently changed or added a new drug to their standard therapy. The temporal relationship between drug administration and the onset of BP is critical, and the culprit drug's withdrawal is the most crucial step toward clinical improvement.

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Introduction

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal blistering disease observed primarily in the elderly (1). Several clinical variants have been described, including classic (bullous), localized, nodular, vegetating, erythrodermic, erosive, childhood, and drug-induced forms. Autoantibodies target the BP230 and BP180 antigens, located in the hemidesmosome complex of the skin basement membrane zone. Subsequent complement activation recruits chemical and cellular immune mediators to the skin, ultimately resulting in blister formation. Both autoantibodies and complement may be detected by various immunofluorescent, immune electron microscopy, and molecular biology techniques (2).

BP usually affects patients over 70 years of age, with an average age of onset between 66 and 83 years. The incidence of bullous pemphigoid ranges between 2.4 and 21.7 new cases per million inhabitants in different populations worldwide. In the United Kingdom, the annual incidence is as high as 42.8 cases per million inhabitants (3). There is a continuous increase in BP incidence, with a 1.9- to 4.3–fold increase in the last two decades. Gender distribution shows a predominance of females in most studies, with a female-to-male ratio between 1.04 and 5.1. Still, after 75 years of age, the incidence is higher in males. Despite the marked increase in incidence, the prevalence is still < 5 per 100,000 population (3).

The reasons driving these increases include an increase in average life expectancy, better diagnostic methods, recognition of atypical variants of BP, and increased use of certain medications (2, 3).

Drug-associated BP (DABP) is a term used to describe cases of BP demonstrating clinical, histological, or immunopathological features

identical or similar to those of the idiopathic form of bullous pemphigoid, but associated with the systemic ingestion or topical application of particular drugs (4).

The purpose of this article is to present a review of the current literature for DABP with a focus on dipeptidyl peptidase 4 (DPP-4) inhibitors.

Drugs associated with bullous pemphigoid

Since the first report of DABP in 1970, in an 11-year-old boy treated with sulfasalazine for ulcerative colitis (5), more than 90 individual drugs were found to be associated with BP (6). As presented in Table 1, these drugs mainly belong to one of the following classes: NSAIDs, salicylates, diuretics, cardiovascular drugs, antibiotics, antidiabetics, neurologic/psychotropics, anti-rheumatics, biologics, and vaccines (6). Systemic psoralens, followed by exposure to ultraviolet rays and topical PUVA, have also been reported to be risk factors for BP.

The association between certain neuroleptics, aldosterone antagonists, and loop diuretics, and BP is well established (4, 7). The use of DPP-4 inhibitors has recently been shown to increase the risk for BP markedly.

Without an accurate medication history, we cannot identify potential DABP. Such a record should consist of a list of all medicines (prescribed and purchased) that a patient was taking before the onset of cutaneous lesions, as well as recent short courses of antimicrobials or NSAIL. Although some patients may not consider these as medicines, the use of herbal remedies, supplements, topical drugs and topical remedies should also be noted. The information should be documented to facilitate the making of valid conclusions.

Table 1. Drugs associated with bullous pemphigoid. Adapted from Verheyden et al. (6)

GROUP	DRUGS ASSOCIATED WITH BULLOUS PEMPHIGOID
NSAIDs	Azapropazone, Celecoxib, Diclofenac, Ibuprofen, Mefenamic acid, Mesalazine, Phenacetin
Salicylates	Aspirin, Sulfasalazine, Salicylazosulfapyride
Cardiovascular	**Ace inhibitors:** Captopril, Enalapril, Lisinopril **Calcium channel blockers:** Amlodipine, Nifedipine **Statins:** Rosuvastatin **Angiotensin II agonists:** Losartan, Valsartan **β-blockers:** Metoprolol **Anticoagulants:** Enoxaparin
Diuretics	Bumetanide, Furosemide, Hydrochlorothiazide, Spironolactone
Antibiotics	Actinomycin D, Amoxicillin, Chloroquine, Flupenthixol, Ciprofloxacin, Griseofulvin, Levofloxacin, Metronidazole, Novoscabin (benzylbenzoate), Penicillin, Rifampicin, Terbinafine
Anti-rheumatics	D-penicillamine, Tiobutarit
Neurologic/Psychotropics	Amantadine, Doxepin, Escitalopram, Fluoxetine, Flupenthixol, Gabapentin, Galantamine hydrobromide, Levetiracetam, Risperidone
Vaccines	Hepatitis B, Herpes zoster virus, Hexavalent combined vaccines, Influenza, Rotavirus, Swine flu, Tetanus
Anti-diabetics	Alogliptin, Anagliptin, Linagliptin, Sitagliptin, Teneligliptin, Vildagliptin
Biologics	**Anti-TNFα:** Adalimumab, Efalizumab, Etanercept, Infliximab **PD-1/PD-L1 inhibitors:** Atezolizumab, Durvalumab, Nivolumab, Pembrolizumab **m-TOR inhibitor:** Everolimus, Sirolimus **Interleukins/IL-antagonists:** Aldesleukin (IL-2), Ustekinumab **Tyrosine Kinase Inhibitors:** Erlotinib **CTLA-4 inhibitors:** Ipilimumab **BRAF inhibitors:** Dabrafenib

Characteristics of drug-induced bullous pemphigoid

The diagnosis can be a clinical challenge since DABP often does not differ from idiopathic BP. However, some clinical features may favor the drug as a trigger factor: I) younger age of onset, II) heterogeneous cutaneous manifestations, III) improvement of the lesions after the withdrawal of the suspected drug (7).

The classic form is characterized by large, tense, serohemorrhagic blisters on an erythematous base. In contrast, in DABP, lesions usually appear on normal-looking skin and may resemble other entities such as erythema multiforme or pemphigus. Patients typically complain of severe pruritus, and Nikolsky's sign may be positive (8). Unlike the classic BP's predominant sites, the DABP may involve the palms, soles, and face (9). Mucosal involvement can occur, although it is quite rare in the classical form of the condition.

It was suggested that some histologic features might assist in diagnosing DABP, including marked eosinophilic infiltrate, intraepidermal vesicles, necrotic keratinocytes, and thrombus formation. Direct and indirect immunofluorescence reveals a similar profile to idiopathic BP, and no specific antigens for DABP have been identified (9).

From the laboratory analyses, a significantly increased number of eosinophils is in favor of DABP.

Other features that support the drug as a trigger factor are resolution following the withdrawal of the supposed drug and the low rates of recurrence.

Mechanisms involved in DABP

The pathogenetic mechanism by which drugs lead to BP is still unknown. It is known that, in those individuals with a genetic predisposition, they lead to an alteration of the immune response (10). One presumed mechanism is by altering the antigenic properties of the basement membrane (BM) by binding to molecules in the basement membrane zone (BMZ), acting as neoantigens, and causing the formation of anti-BMZ antibodies (5, 11). They can also structurally alter molecules and detect previously hidden epitopes, which also stimulate the immune response (8, 12).

Also, an induced reaction from one drug may lead to a cross-reaction with another drug in the same group (13). Through interaction with sulfur groups in BMZ, sulfur-containing drugs in their structure can lead to direct damage without involving the immune system (10, 14).

Dipeptidyl peptidase-4 inhibitors

There is a growing body of evidence of an association between dipeptidyl peptidase-4 inhibitors (DPP-4i) and the risk of developing BP (2–7).

DPP-4i or gliptins are a class of oral hypoglycaemic drugs that are used for the treatment of diabetes mellitus type 2, especially in the adult population.

Dipeptidyl peptidase-4 (DPP4), also called CD26, is a protein found on the surface of most cells. It plays a key role in immune system regulation, cell signaling, and programmed cell death (apoptosis). DPP-4 is an enzyme serine exopeptidase that cleaves X-proline and X alanine dipeptides from the N-terminus of polypeptides (15).

DPP4 participates in glucose metabolism through inactivation of incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Incretins are metabolic hormones that are released after eating. On one hand, they increase insulin secretion, while on the other hand, they decrease the release of GLP-1, two mechanisms that lead to decreased glycemia. Both GLP-1 and GIP are immediately inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), so DPP4 inhibitors prolong the physiological function of incretins (16).

Sitagliptin, the first DPP-4i was approved by the FDA in 2006, followed by dozens of others, including saxagliptin, linagliptin, and alogliptin (FDA) (17), vildagliptin (EU) (18), anagliptin (19) and teneligliptin (Japan).

DPP4i associated bullous pemphigoid

Since the first five reported cases of DPP4i-BP in 2011 (20), the association of glyptins as inducers of BP development has been reported in numerous case studies and case series. The most common inductors are vildagliptin (20–32), sitagliptin (20, 28, 32), linagliptin (23, 28, 32), anagliptin (33), and alogliptin (28). This association has been further confirmed in large-scale studies of several national drug adverse reactions databases in France (34), European Pharmacovigilance (24), Japan (35), Finland (36), and in controlled observational studies in France and Switzerland (37), Israel (38), South Korea (39) and France (40).

Clinical, immunological and pathological features of gliptin-associated BP have been reported to be distinct, compared to classic BP. Patients with DPP-4 inhibitor-induced BP may present either an inflammatory or a noninflammatory phenotype of BP (41), more severe blistering, and erosive lesions (42). A non-inflammatory phenotype with less erythema, fewer urticarial lesions and fewer eosinophils in skin lesions has also been reported in Japanese populations (43). Patients with DPP-4i-associated BP may be presented with an extensive mucosal involvement (38).

IgG antibody response against other BP180 regions different from the NC16A domain (41, 43), and a case with anti BP230 antibody DPP-4i induced BP were reported (30). Patients receiving DPP-4i treatment may show different DIF patterns than DIF in classic BP (44). The association between gliptin-associated BP and HLA-

DQB1*03:01 was reported by Japanese patients (45), but no such association was found in the Finnish study (46).

Although significant progress has been made, the precise pathogenesis of the association between DPP4i and BP remains unclear. There are several presumed pathogenetic mechanisms such as the expression of antigens on the surface of many different cell types in the human body, including T lymphocytes, as well as different cell types in the skin and subcutaneous tissue (47).

One presumed pathogenetic mechanism is the association between DPP-4 inhibitors and BP via the eotaxin CCL11/CCR3 axis. Namely, among other cytokine substrates of this enzyme under physiological conditions, its substrate is also eotaxin (CCL11), which through its protease activity inactivates the enzyme and consequently this inactivation leads to activation and infiltration of eosinophils in the skin, tissue damage and possible formation of blisters (48). Another possible pathogenetic mechanism is the plasmin activity on NC16A from BP180. DPP4 is a plasminogen receptor expressed on the cell surface, which activates the plasminogen with subsequent plasmin formation (49). Plasmin leads to cleavage of the NC16A immunodominant domain from BP180 to 120 kD and 97 kD ectodomains, i.e. new epitopes for DPP4i-BP autoantibodies (50).

DPP-4i may influence keratinocytes in an epithelial-mesenchymal transition (EMT)-dependent manner. An EMT is a biological process that allows a polarized epithelial cell, which normally interacts with the basement membrane via its basal surface, to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype (51). EMT may exert an effect on various basement membrane proteins including BP180.

In the presence of gliptins modifications in the activity of allied proteases, like the highly homologous seprase (52) with marked gelatinase activity, might affect the epidermal basement membrane zone (53).

DPP4i-BP is a newly recognized autoimmune blistering disease. While DPP4 inhibitors (DPP4i) are known to act as a trigger, the underlying mechanisms of the disease remain unclear and require further investigation.

Conclusion

BP is the most common autoimmune bullous dermatosis, especially in elderly patients, with a growing incidence in the last two decades. There is an ongoing list of medications that have been incriminated to trigger BP formation. DPP4i are of particular importance, not only because they are mostly used in the risk groups for BP, but because it has been proven that they cause DAPB. Hence, in a patient with BP, practitioners should always rule out any medication trigger factors and hold back with introductions of new drugs, especially ones that are proven to cause DABP. Obtaining an accurate medication history is the first step in the diagnosis of DABP. DABP must always be considered as a possible diagnosis in elderly patients who have recently changed or added a new drug to their regular medication regimen, because it usually resolves after withdrawal of the suspected medication, with very good therapeutic response, and fewer or no recurrences.

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BULOZNI PEMFIGOID INDUKOVAN INHIBITORIMA DIPEPTIDIL PEPTIDAZE-4: PREGLED TRENUTNIH SAZNANJA

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Bulozni pemfigoid (BP) predstavlja hroničnu autoimunu bolest koja podrazumeva stvaranje mehurova ispod epidermisa, a pretežno se javlja kod starijih ljudi. U poslednje dve decenije zabeležen je značajan porast incidencije i prevalencije BP-a u većem broju zemalja širom sveta. Kao uzroci tog porasta mogli bi se navesti produženje očekivanog životnog veka, unapređene dijagnostičke metode, prepoznavanje atipičnih varijanti BP-a i povećana upotreba određenih lekova.

Lekovima izazvan BP (engl. *drug-associated bullous pemphigoid* – DABP) jeste termin koji se koristi za opisivanje slučajeva BP-a koji pokazuju kliničke, histološke ili imunopatološke karakteristike koje su identične sa idiopatskim oblikom BP-a ili su mu slične, a povezani su sa sistematičnom primenom ili lokalnom aplikacijom određenih lekova. Od prvog izveštaja o DABP-u iz 1970. godine do sada, sa BP-om je povezano više od 90 pojedinačnih lekova. Najsnažniji dokazi o povezanosti sa DABP-om zabeleženi su kod inhibitora dipeptidil peptidaze-4, poznatih i kao gliptini, koji predstavljaju relativno novu klasu oralnih antidijabetika.

Na DABP treba posumnjati kod bolesnika kojima je nedavno promenjena ili dodata nova terapija. Vremenska povezanost između primene leka i pojave BP-a od ključnog je značaja, a povlačenje sumnjivog leka predstavlja najvažniji korak ka kliničkom poboljšanju.

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***Ključne reči**: pemfigoid, bulozni, inhibitori dipeptidil peptidaze-4, vildagliptin, dijabetes melitus*